Kunutsor, S. K., Khan, H., Nyyssönen, K., & Laukkanen, J. A. (2016). Is lipoprotein (a) protective of dementia? *European Journal of Epidemiology*, *31*(11), 1149-1152. https://doi.org/10.1007/s10654-016-0184-0

Is lipoprotein (a) protective of dementia?

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Word count [1,337]

Number of references [15]

Number of figures [1]

Number of tables [1]

Abstract

Lipoprotein(a) [Lp(a)] - an established risk factor for vascular disease, has been suggested to be associated with risk of dementia**,** however no prospective evidence exists to support this finding. We aimed to assess the association of lipoprotein(a) [Lp(a)] with dementia risk. Lp(a) concentration was assessed at baseline in a prospective cohort of 2,532 men aged 42-61 years. During a median follow-up of 24.9 years, 228 new cases of dementia were recorded. Lp(a) was approximately log-linearly associated with dementia risk. In age-adjusted analysis, the hazard ratio for dementia in a comparison of extreme quartiles of Lp(a) levels was 0.68 (95% CI: 0.47-0.99), which persisted after adjustment for several physical measures, history of coronary heart disease, smoking status, history of diabetes, serum lipids, alcohol consumption, and socio-economic status 0.68 (0.46-0.99). Lp(a) is protective of future dementia risk in a middle-aged male Caucasian population. Further research is needed replicate these findings.

Keywords: Lipoprotein(a); risk factor; dementia

Introduction

Dementia is a growing public health concern especially with an aging population.(1) Though ageing and the *APOE* gene (encoding apolipoprotein E, ApoE) are major risk factors for dementia,(2) its pathogenesis is still not fully understood. Lipoprotein (a) [Lp(a)], which consists of a low-density lipoprotein (LDL)-like core lipoprotein covalently linked to glycoprotein Apo(a),(3) is a causal risk factor for vascular disease; (4) which is known to be associated with cognitive decline.(5) Emerging evidence suggests Lp(a) may be linked with the development of dementia. However, data on the association between Lp(a) and risk of dementia are sparse and inconsistent. Whereas some studies have shown higher levels of Lp(a) to be linked with increased dementia risk,(6) some have shown a protective effect,(6-8) and others have shown no association at all.(9) However, due to the case-control design of these previous studies, the temporal sequence of the relationship between Lp(a) and cognitive decline has not been established and whether elevated Lp(a) levels increase or decrease the risk of future dementia is currently unknown. In this context, our aim was to assess the prospective nature of the association between plasma Lp(a) and risk of dementia in a population-based cohort of 2,532 apparently healthy middle-aged men from eastern Finland.

Methods

Participants in the study were men aged 42-61 years recruited into the Kuopio Ischemic Heart Disease (KIHD) study in eastern Finland, previously described.(10) The Research Ethics Committee of the University of Eastern Finland approved the study, and each participant gave written informed consent. Lipoprotein(a) concentrations were measured from frozen plasma samples stored at -20° C for 2-6 years, using a radioimmunoassay (Mercodia Apo(a) RIA, Mercodia AB, Uppsala, Sweden). Details on dementia screening and diagnosis have been described in a recent report.(10) Briefly, participants were first screened using the Mini-Mental State Examination and Geriatric Mental State at baseline examination and every year, followed by further cognitive testing of screen-positives. An independent committee of neurologists of the KIHD study, masked to clinical data, reviewed all potential cases of

dementia to obtain a consensus on the diagnosis and aetiology. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

The mean age at entry was 53 (SD, 5) years. The median (interquartile range) of Lp(a) at baseline was 9.66 (3.78-22.56) mg/dl. During a median follow-up of 24.9 years, 228 dementia cases were recorded. In analysis adjusted for conventional risk factors, there was an approximately log-linear association of Lp(a) with incident dementia (**Figure**). In age-adjusted analysis, the HR for dementia comparing the top quartile with the bottom quartile of baseline $\log_e$ Lp(a) levels was 0.68 (95% CI: 0.47 to 0.99; P =0.044). The association remained consistent on further adjustment for body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity 0.68 (95% CI: 0.46 to 0.99; P = 0.044). These findings remained unchanged after accounting for incident coronary events (**Table**). The total number of all-cause mortality events recorded during follow-up was 1202, of which 559 were CVD deaths. In analyses that adjusted for all-cause mortality and CVD mortality as competing risk events, the HR for dementia was 0.91 (95% CI: 0.47 to 1.76; P = 0.781) and 0.71 (95% CI: 0.46 to 1.10; P = 0.124) respectively. In subsidiary analyses, we found suggestions of positive associations of Lp(a) with all-cause mortality and CHD, but the associations were less robust; 1.07 (95% CI: 0.91 to 1.25; P = 0.423) and 1.18 (95% CI: 0.97 to 1.43; P = 0.100) respectively.

Comment

In this population-based prospective study of middle-aged Finnish men, we found an approximately log-linear inverse and independent association between Lp(a) and dementia risk. However, given the high mortality rate in our study cohort which might have hindered our event of interest, the association was attenuated when all-cause and CVD mortality were adjusted for as competing risk events. Though the

pathogenesis of dementia is not completely understood, mechanistic research provides strong support for inflammatory and oxidative pathways.(11) Vascular disease is a well-recognised risk factor for dementia(5) and given the established role of elevated Lp(a) levels in the pathogenesis of vascular disease,(4) there are suggestions that increased Lp(a) levels may be associated with an increased risk of dementia. It therefore appears that the inverse association demonstrated in the present study is at odds with the biologically plausibility of the relationship. However, given the inconsistent evidence and controversy surrounding the relationship between Lp(a) and dementia, this may not be the case. Mooser and colleagues in a case-control study design, reported an increased risk of late-onset Alzheimer's disease with elevated Lp(a) levels in ApoE4 carriers, with a reduced risk seen among older noncarriers of ApoE4.(8) In a similar case-control design, Iwamoto and colleagues also demonstrated a protective effect in elderly patients, but who were ApoE4 carriers. In another case-control design, Solfrizzi and colleagues showed a protective effect of Lp(a) among elderly patients.(6) The prospective nature of our study conducted in middle-aged cognitively healthy individuals at baseline offsets some of the biases in these previous studies and decreases the likelihood of reverse causality. However, there is a possibility that our results may have been overestimated, given that that the association was attenuated when competing risks were taken into account.

It has been speculated that the protective effect of Lp(a) on dementia could be due to the Apo(a) gene,(7) which is a major determinant of plasma Lp(a) levels.(12) Sarti and colleagues postulated that older individuals carry the less harmful type of Lp(a) and therefore are protected from its putative detrimental effect on cognitive function.(9) In addition, since there might be a link between ApoE and Lp(a) metabolism, there is a speculation that Apo(a) alters ApoE isoform metabolism which suppresses changes related to the development of dementia.(7) The levels of Lp(a) in cerebrospinal fluid have been found to correlate strongly with plasma levels,(13) suggesting a possible role of Lp(a) in lipoprotein metabolism in the central nervous system and the development of neurological disorders. Just like ApoA-I, which has been found to have a protective effect on dementia risk,(14) Lp(a) may be directly involved in the pathology of dementia by participating in amyloidogenesis and playing a role in neuronal

maintenance.(15) Our findings are relevant as they indicate that elevated Lp(a) levels might be protective of the risk of dementia. However, given the paradoxical nature of the present findings and obvious limitations such as (i) low event rate; (ii) lack of generalizability of our findings because the study population included middle-aged Caucasian men and therefore cannot necessarily be extrapolated to women, other age groups and ethnicities; and (iii) lack of complete genetic data, which precluded further analyses such as adjusting for ApoE, a major genetic risk factor for age-related cognitive decline; (2) further studies are needed to replicate these results. Strengths of this study include: (i) the large sample that was selected to be a nationally representative population-based sample of middle-aged men; (ii) the high participation rate and no losses during follow-up; (iii) a long mean follow-up period; and (iv) adjustment for a comprehensive panel of potential confounders.

In conclusion, Lp(a) is log-linearly and inversely associated with future risk of dementia in this middle-aged Finnish male population. Further research is however needed to replicate these findings and help unravel the mechanistic pathways linking Lp(a) and the risk of dementia.

Acknowledgments

We thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland for the data collection in the study.

Funding

This work was supported by the Academy of Finland, Helsinki, Finland; Finnish Foundation for Cardiovascular Research, Helsinki, Finland, and Finnish Cultural Foundation, Helsinki, Finland. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflict of interest

The authors declare they have no conflict of interest.

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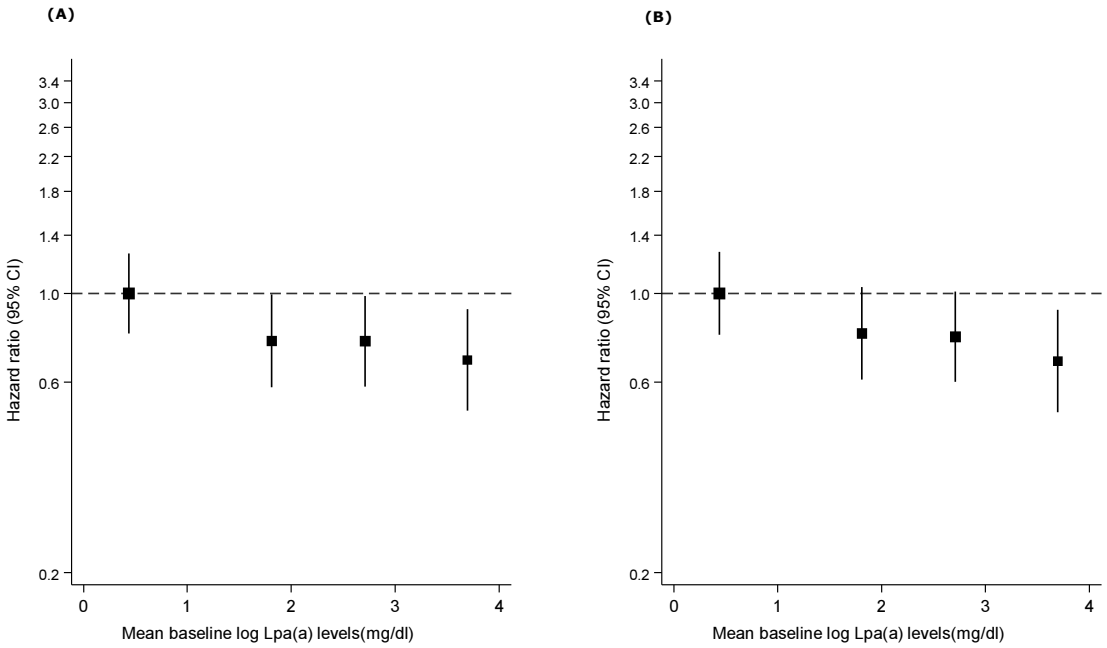
Figure Legends

Figure. Hazard ratios for dementia, by quartiles of baseline levels of lipoprotein(a)



A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity

Table. Association of baseline lipoprotein(a) with dementia

	Events/Total	**Model 1**		**Model 2**		**Model 3**	
Lipoprotein(a) quartiles (mg/dl)		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Quartile 1 (0.56-3.78)	72 / 637	Ref		Ref		Ref	
Quartile 2 (3.81-9.65)	54 / 629	0.76 (0.53 to 1.08)	0.129	0.79 (0.56 to 1.14)	0.208	0.79 (0.55 to 1.13)	0.195
Quartile 3 (9.66-22.53)	57 / 633	0.76 (0.54 to 1.07)	0.119	0.78 (0.55 to 1.11)	0.165	0.77 (0.54 to 1.10)	0.155
Quartile 4 (> 22.53)	45 / 633	0.68 (0.47 to 0.99)	0.044	0.68 (0.46 to 0.99)	0.044	0.68 (0.46 to 0.99)	0.045

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity

Model 3: Model 3 plus incident coronary heart disease as a time-dependent covariate